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The major accomplishments in the course of the last 5 years have been to clarify the metabolic alterations that accompany endotoxin shock, primarily with regard to glucose turnover and gluconeogenesis from lactate and alanine. Also, the alterations in myocardial substrate utilization have been identified, and the significance of substrate preference characterized following endotoxin administration. Furthermore, a useful and physiologically sound isolated myocardial cell preparation has been developed which

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enables us to further investigate the sub-cellular effects of both cardiac depressant factors and also cardiotonic agents. Although much has been accomplished, it is quite clear that many features of the exact sub-cellular defects caused by endotoxin administration, or any other form of shock, still remain to be learned.

FINAL REPORT ON WORK PERFORMED UNDER ONR CONTRACT N00014-76-C-0132, (1975-80).
By John J. Spitzer, M.D.

Although a number of seemingly different studies have been performed under this contract during the last 5 years, the major theme of investigation was aimed at a better understanding of cellular and sub-cellular damage in the myocardium and other tissues during shock. The following is a summary of the progress in the various areas of investigation:

1.) The majority of the progress during the last 5 years has been in the area of the deleterious effects of shock on myocardial metabolism. The studies have been conducted on various levels of organization: On the cellular and sub-cellular levels, as well as on the level of the whole organism. The results revealed that in the course of shock (whether produced by the administration of endotoxin, or by excessive hemorrhage) a major alteration in substrate utilization by the myocardium is produced consisting of a decreased oxidation of fatty acids and an increased utilization of lactate. These changes can be reproduced not only under in vivo conditions, but also in vitro, by the addition of varying concentrations of E. Coli endotoxin. Although we have not been able to determine the exact molecular mechanism of this derangement as yet, we have been able to ascertain the fact that changes in substrate utilization are not due to either the altered transport of fatty acids or glucose following endotoxin administration. Thus the translocation of these metabolites is unaffected by shock and, therefore, the cytosolic or mitochondrial locations are the two sites to be investigated next. In order to study the sub-cellular damage of myocardial metabolism, however, it is necessary to develop a single cell preparation in which this problem can be investigated relatively easily. Therefore, we turned our attention to the development of an isolated myocardial cell preparation, which would behave in a physiologic manner and, in which the effect of various cardiac depressant and cardiac stimulant agents could be investigated. Therefore, we have developed a myocardial cell preparation which is reproducable, gives us a good yield, is

viable over the necessary period of time, and is also tolerant to the presence of physiologic concentration of calcium ions. These cells are expected to serve as excellent tools in further studies. We consider the achievement of obtaining these useful myocytes a major progress in our studies and are now utilizing this cell preparation for investigation such noxious agents as hypoxia and ischemia, as well as such potentially useful compounds as PGB_X.

2.) Participation of the changes in insulin secretion and inactivation as well as glucagon secretion in the metabolic response to injury. We and other investigators have ascertained that following trauma, injury, or during shock, the plasma concentration of glucagon is greatly elevated while that of insulin may not be altered or is slightly increased. Therefore, it was of interest to further investigate the effects of shock on the secretion of these hormones by the pancreas. In these studies we have found that endotoxin administration sensitizes the pancreas to the physiologic stimulus of insulin secretion, i.e. glucose. Thus, following glucose administration in the endotoxin treated animals, the pancreas responded with a greatly elevated insulin release. We also studied the inactivation of insulin under these conditions and found that both under in vivo and in vitro conditions, the rate of inactivation of insulin was not altered. Thus, the hyperinsulinemia following glucose administration in endotoxicosis is a phenomenon due to alteration of pancreatic β-cells to the physiologic signal, glucose.

3.) Changes in glucose turnover following endotoxin administration. Glucose turnover is increased initially and remains at, or above normal level for several hours following endotoxin administration. This finding indicates that gluconeogenesis is able to keep pace with the increased peripheral utilization of this metabolite and represents a remarkable adaptation by the organism to the

altered demands imposed by the pathologic insult. On the other hand, we have also observed, that preterminally the gluconeogenic ability of the organism fails and thus, glucose turnover decreases resulting in pathologically low glucose concentrations (15-20 mg/dl). Such low plasma glucose concentrations are not able to supply the central nervous system with the minimum requirements of this metabolite.

4.) Changes in the contribution of lactate and alanine to gluconeogenesis during shock. In the animal in shock, gluconeogenesis is primarily maintained from lactate, a metabolite which is released from the periphery in greater than normal quantities under these conditions. The major site of gluconeogenesis under these conditions is the liver. Alanine also contributes to this process but in a quantitatively lesser degree. We have found that the turnover of lactate was greatly elevated following endotoxin administration, which is not only of potential survival value as a supplier of gluconeogenic substrate, but also serves as an alternative oxidative substrate for the myocardium under these conditions (see Item NO. 1 of this report). This is another example of physiologic adaptation to adverse conditions. As long as the adaptive mechanisms are operative, useful compensation takes place. Whenever the adaptive mechanisms fail, irreversible damage is inflicted. Thus, a better understanding of the above-discussed responses are important, if we hope to prevent shock and trauma to cause irreversible damage.

5.) Alterations in myocardial metabolism in diabetic animals during shock. A preliminary has also been undertaken to investigate the alterations of myocardial metabolism in diabetic animals. We have found both under *in vivo* conditions and also *in vitro*, in myocardial homogenates, that the heart of diabetic animals is not readily able to utilize lactate as a major metabolite for its metabolic needs. This may have practical implications, as the organism which is in shock

abounds in lactate, which under normal conditions is able to replace fatty acids as the maj substrates for myocardial metabolism. This, however, is not the case in the diabetics and therefore, a major defect in myocardial function may arise from the inability of the heart to oxidize lactate.

In conclusion, the major accomplishments in the course of the last 5 years have been to clarify the metabolic alterations that accompany endotoxin shock, primarily with regard to glucose turnover and gluconeogenesis from lactate and alanine. Also, the alterations in myocardial substrate utilization have been identified, and the significance of substrate preference characterized following endotoxin administration. Furthermore, a useful and physiologically sound isolated myocardial cell preparation has been developed which enables us to further investigate the sub-cellular effects of both cardiac depressant factors and also cardiotonic agents. Although much has been accomplished, it is quite clear that many features of the exact sub-cellular defects caused by endotoxin administration, or any other form of shock, still remain to be learned.

Further details of our research accomplishments may be obtained through the perusal of the following list of publications that resulted from the last 5 years of ONR support:

1.) Spitzer, J.J., Bechtel, A.A., Archer, L.T., Black, M.R., Greenfield, L.J., Hinshaw, L.B., Effects of coronary hypotension on myocardial substrate utilization, Am. J. Physiol., 228. 365-368, 1975.

2.) Schwarz, H.P., Spitzer, J.J., Dreisbach, L., Effect of norepinephrine on the phospholipid composition of blood plasma and red blood cells in anesthetized dogs, Physiol. Chem. and Physics, 8. 53-59, 1976.

3.) Spitzer, J.J., Wagner, G.G., Blackard, W.G., The Effect of glucose infusion on selected hemodynamic and metabolic variables and on plasma insulin concentration in dogs after Escherichia coli endotoxin administration, Circ. Shock, 3. 31-38, 1976.

4.) Spitzer, J.J., Greenfield, L.J., Hinshaw, L.B., Effects of prolonged coronary hypotension on myocardial substrate utilization, Recent Advances on Cardiac Structure and Metabolism, 10. 235-239, 1975.

5.) Spitzer, J.J., Hinshaw, L.B., Myocardial substrate utilization in experimental shock, Circ. Shock, 2. 137-142, 1975.

6.) Wolfe, R.R., Elahi, D., Spitzer, J.J., Glucose and lactate kinetics after endotoxin administration on dogs, Am. J. Physiol, 232. E180-E185, 1977.

7.) Liu, M.S., Spitzer, J.J., In vitro effects of E. Coli endotoxin on fatty acid and lactate oxidation in canine myocardium, Circ. Shock, 4. 181-190, 1977.

8.) Liu, M.S., Spitzer, J.J., Myocardial fatty acid and lactate metabolism after E. Coli endotoxin administration, Circ. Shock, 4. 191-200, 1977.

9.) Wolfe, R.R., Elahi, D., Spitzer, J.J., Glucose kinetics in dogs following a lethal dose of endotoxin, Metabolism, 26. 847-850, 1977.

10.) Liu, M.S., Spitzer, J.J., Oxidation of palmitate and lactate by beating myocytes isolated from adult dog heart, J. Mol. Cell. Card., 10. 415-426, 1978.

11.) Kuttner, R.E., Spitzer, J.J., Gluconeogenesis from alanine in endotoxin-treated dogs, J. Surg. R., 25. 166-173, 1978.

12.) Liu, M.S., Spitzer, J.J., Fatty acid and lactate metabolism by heart homogenates from alloxan-diabetic dogs, Horm. Met. Res., 10. 114-117, 1978.

13.) Fritschka, E., Ferguson, J.L., Spitzer, J.J., Increased fatty acid turnover in CSF during hypotension in dogs, Am. J. Physiol., 236. H802-H807, 1979.

14.) Kuttner, R.E., Spitzer, J.J., The effect of endotoxin on plasma-aminoisobutyric acid, Experientia, 36. 215-216, 1980.

15.) Long, W.M., Bagby, G.J., Spitzer, J.J., Contribution of viable and nonviable heart mycoytes to substrate oxidation, Am. J. Physiol., 238. H740-H744, 1980.

16.) Spitzer, J.J., Lipid metabolism in endotoxic shock, Circ. Shock, 1. 69-79, 1979.

17.) Fritschka, E., Ferguson, J.L., Spitzer, J.J., Total and regional cerebral blood flow during perfusion from the lateral ventricle to the cisterna magna in the concious dog, Circ. Shock, 7. 333-342, 1980.

18.) Romanosky, A.J., Bagby, G.J., Bockman, E.L., Spitzer, J.J., Increased muscle glucose uptake and lactate release following endotoxin administration, Am. J. Physiol. in press.

19.) Romanosky, A.J., Bagby, G.J., Bockman, E.L., Spitzer, J.J., Free fatty acid utilization by skeletal muscle following endotoxin administration, Am. J. Physiol. in press.

20.) Liu, M.S., Long, W.L., Spitzer J.J., Effect of E. coli endotoxin on palmitate, glucose, and lactate utilization by isolated dog heart myocytes, accepted for publication in J.A. Majde and R.J. Person: The Pathology of Endotoxin at the Cellular Level.

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The following is an index of technical reports issued under this contract:

1.) Fatty Acid and Lactate Metabolism by Heart Homogenates from Alloxan-Diabetic dogs by M.S. Liu and J.J. Spitzer.

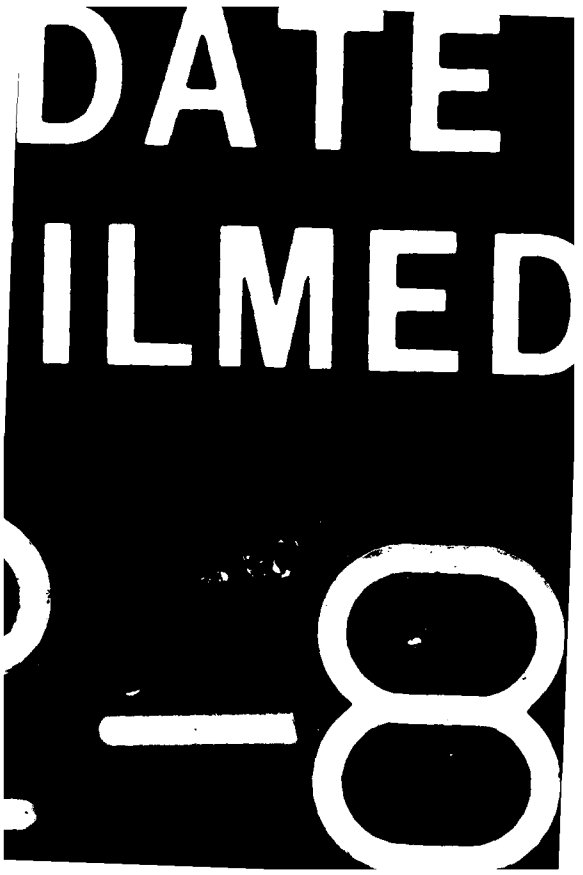
2.) Oxidation of Palmitate and Lactate by Beating Myocytes Isolated from Adult Dog Heart by M.S. Liu and J.J. Spitzer.

3.) Gluconeogenesis from Alanine in Endotoxin-Treated Dogs by R.E. Kuttner and J.J. Spitzer.

4.) Effect of Moderate Hemorrhagic Hypotension on Cerebral Metabolism During Ventriculocisternal Perfusion in the Concious Dog by E. Fritschka, J.L. Ferguson and J.J. Spitzer.

5.) Lipid Metabolism in Endotoxic Shock by J.J. Spitzer.

6.) Increased Fatty Acid Turnover in CSF During Hypotension in Dogs by E. Fritschka, J.L. Ferguson, and J.J. Spitzer.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